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# Synthesis and characterization of highly functionalized symmetric aromatic hexa-ol intermediates from oleic acid

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ABSTRACT

A novel highly functionalized aromatic hexa-ol was synthesized by palladium-catalyzed cyclotrimerization of an alkyne fatty acid ester followed by LAH reduction. This polyol product is a novel monomer made from a renewable lipid raw material for the production of polyurethanes, polyesters and polyamides.

## 1. Introduction

Oleochemistry has attracted significant interest in the chemistry community since oils and fats are renewable, abundant and environmentally friendly. Through chemical modification, oleochemical feedstocks are converted into a wide range of products, such as soaps, lubricants, food additives, etc. In the 1980s, oleochemical reactions were mainly focused on the carboxyl group of fatty acids (Baumann et al., 1988) for example hydrolysis of fats to make soaps (Sonntag, 1982) and synthesis of fatty amines from fatty acids (Billenstein and Blaschke, 1984). Recently, significantly more interest has been focussed on the hydrocarbon chains of fatty acids, especially the alkene moiety of unsaturated fatty acids (Biermann and Metzger, 2004). A large number of novel fatty compounds have been synthesized through modification of these carbon–carbon double bonds. Aliphatic polyols are one of the most successful class of products to derive from such efforts. Epoxidation of alkenes in unsaturated fatty acids followed by nucleophilic ring opening of the epoxide has been utilized to produce polyols. These polyols have been used as monomers for the production of useful polyurethanes (Guo et al., 2000). Our research group has also developed methodology utilizing ozonolysis of alkenes, followed by catalytic hydrogenation to produce polyols from vegetable oils (Narine et al., 2007), which were then used to synthesize polyurethane elastomers and foams (Kong and Narine, 2007; Kong et al., 2007).

Transition metal-catalyzed trimerization of alkyne fatty acid compounds provides an alternative method for the preparation of highly functionalized aromatic polyols. Since Reppe and Schweckendiek reported the first cyclotrimerization of acetylene in 1948 with nickel as a catalyst to yield benzene derivatives (Reppe and Schweckendiek, 1948), various transition metal catalysts for cyclotrimerization have been reported. Among these catalysts, palladium is the most commonly used. In 1987, Jhingan and Maier reported a simple way to make substituted benzenes in the presence of Pd/C (Jhingan and Maier, 1987). This methodology has since been applied in the cyclotrimerization of long chain alkyne fatty acid compounds by a number of research groups. Augustin performed some unpublished work where aromatic polyols were produced by cyclotrimerization of alkyne fatty acid material (Biermann et al., 2000). In 1990, Renga et al. patented an approach to producing hexa-substituted benzene derivatives from alkyne fatty alcohols, acids and esters (Renga et al., 1990). The trimer products were a mixture of symmetric and asymmetric isomers. Galia and co-workers have synthesized aromatic triols from the esters of oleic acid, but have reported that the mixture of symmetric and asymmetric triols were inseparable (Lligadas et al., 2007). Recently, our group has successfully isolated and characterized these two triol isomers (Yue and Narine, 2008). All these previous studies on the cyclotrimerization of fatty alkynes utilized

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asymmetric alkynes with one terminal functional group. That resulted in a mixture of symmetric and asymmetric hexa-substituted benzene derivatives with three terminal functionalized groups and three unfunctionalized alkyl groups. These three unfunctionalized alkyl groups become dangling chains in any further polymerization reactions. Since these unsupported dangling chains do not support stress, these would significantly affect the mechanical properties of resulting polymers. We report here an approach to synthesize a single highly symmetric aromatic hexa-ol from symmetric fatty acid alkyne derivatives, to produce fully functionalized groups around the aromatic ring omitting any dangling alkyl chains. This novel polyfunctional hexa-ol is a novel potential monomer for the production of polyurethanes, polyesters and polyamides with interesting properties.

## 2. Experimental

Oleic acid (90%), and all other chemicals and reagents were purchased from Sigma–Aldrich Co., USA. Silica gel (230–400 mesh) was obtained from Rose Scientific Ltd., AB, Canada. TLC plate (250 μm) was obtained from Silicycle Chemistry Division, QC, Canada. FTIR spectra were measured with a Mattson Galaxy Series FT-IR 3000 spectrophotometer. $^1H$ NMR and $^{13}C$ NMR were recorded on Varian 500 MHz spectrometers (Varian, Inc., California, USA) with $CDCl_3$ or $CD_3OD$ as a solvent. Mass spectra were acquired on a Mariner Biospectrometry ESI system (PerSeptive Biosystems Inc., Massachusetts, USA) or Kratos Analytical MS-50 (Kratos Analytical Ltd., Manchester, UK) EI high-resolution spectrometer.

### *2.1. Unsaturated-α,ω-dicarboxylic acid* ***2***

To oleic acid (100.0 g, 319.0 mmol) was added Grubbs catalyst (second generation) (27 mg, $3.19 \times 10^{-2}$ mmol) under the protection of nitrogen. The solution was stirred by mechanical stirrer and heated to 45 °C. After an hour, the solution became cloudy. The reaction was further stirred for 14 h to obtain a white sticky solution. Then ethyl vinyl ether (5 mL) was added and the mixture allowed to stir for half an hour to quench the Grubbs catalyst. The mixture was recrystallized twice from hexanes (300 mL) and EtOAc (50 mL) to afford a white power as the product (26.4 g, 53% yield). IR (Microscope) 3200–2500 (OH of carboxylic acid), 1697 (C=O) $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$ 5.39–5.36 (m, 2H, CH=CH), 2.27 (t, 4H, $J = 7.4$ Hz, $CH_2$–COOH), 1.99–1.94 (m, 4H, $CH_2$–CH=CH), 1.59 (quintet, 4H, $J = 7.4$ Hz, $CH_2$–$CH_2$COOH), 1.38–1.26 (m, 18H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta$ 177.7 (C=O), 131.5 (CH=CH), 34.9, 33.6, 30.7, 30.24, 30.22, 30.0, 26.1; HRMS (ESI) calcd for $C_{18}H_{31}O_4$ ($[M-H]^-$) 311.2217, found: 311.2214.

### *2.2. Dibromide-α,ω-dicarboxylic acid* ***3***

To the solution of unsaturated diacid **2** (19.0 g, 60.8 mmol) in diethyl ether (300 mL) was added bromine (3.8 mL, 73.0 mmol) dropwise *via* addition funnel over 30 min. The solid dissolved and the solution became light red. The solution was stirred for another 30 min. Then saturated sodium thiosulfate (20 mL) was added to reduce any excess bromine. The resulting organic phase was separated and washed with brine (20 mL) and dried over $MgSO_4$. The ether solvent was evaporated under reduced pressure. The resulting solid was crystallized with hexanes (200 mL) and EtOAc (200 mL) to give a white powder as the product (24 g, 83% yield). IR (Microscope) 3200–2500 (OH of carboxylic acid), 1693 (C=O) $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$ 4.29–4.23 (m, 2H, CH–Br), 2.30 (t, 4H, $J = 7.4$ Hz, $CH_2$–COOH), 2.15–2.07 (m, 2H, CH–CHBr), 1.98–1.90 (m, 2H, CH–CHBr), 1.68–1.56 (m, 6H), 1.50–1.28 (m, 14H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta$ 177.6 (C=O), 61.3 (CH–Br), 37.8, 34.9, 30.2, 30.1, 29.8, 28.1, 26.1; HRMS (ESI) calcd for $C_{18}H_{31}O_4Br_2$ ($[M-H]^-$) 469.0584, found: 469.0593.

### *2.3. Alkyne-α,ω-dicarboxylic acid* ***5/6***

Dibromide compound **3** (1.0 g, 2.12 mmol) was dissolved in DMSO (20 mL). Potassium *tert*-butoxide (2.37 g, 21.2 mmol) was then added. The reaction mixture was heated at 100 °C for 2 h. Then the solution was poured into 2N HCl (60 mL) at room temperature. The precipitate was filtered, washed with water and dried over the air to give crude light yellow solid **5/6** (520 mg, 83% yield). IR (Microscope) 3100–2500 (OH of carboxylic acid), 1688 (C=O) $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$ 2.27 (t, 4H, $J = 7.4$ Hz, $CH_2$–COOH), 2.11 (t, 4H, $J = 6.6$ Hz, $CH_2$–CC), 1.59 (quintet, 4H, $J = 7.4$ Hz, $CH_2$–$CH_2$COOH), 1.50–1.28 (m, 16H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta$ 177.7 (C=O), 80.9 (CC), 34.9, 30.2 (two carbon overlap), 29.9, 29.7, 26.1, 19.4; HRMS (ESI) calcd for $C_{18}H_{29}O_4$ ($[M-H]^-$) 309.2060, found: 309.2058.

### *2.4. Alkyne-α,ω-dicarboxylic ester* ***7***

To a solution of diacid **5/6** (520 mg, 1.68 mmol) in methanol (20 mL) was added one drop of concentrated sulphuric acid. The reaction mixture was refluxed for 1 h. The solvent was evaporated under the reduced pressure and the residue was purified by column chromatography to afford alkyne ester **7** (381 mg) and allene ester **8** (142 mg) as colorless oils.

IR (Microscope) 1741 (C=O) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 3.66 (s, 6H, $CH_3$–O), 2.30 (t, 4H, $J = 7.4$ Hz, $CH_2$–COOH), 2.12 (t, 4H, $J = 7.0$ Hz, $CH_2$–CC), 1.65–1.58 (quintet, 4H, $J = 7.4$ Hz, $CH_2$–$CH_2$COOH), 1.46 (quintet, 4H, $J = 6.9$ Hz, $CH_2$–CC), 1.40–1.22 (m, 14H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 174.2 (C=O), 80.1 (CC), 51.4 ($CH_3$–O), 34.1, 29.05, 29.03, 28.8, 28.6, 24.8, 18.7; HRMS (ESI) calcd for $C_{20}H_{34}O_4Na$ ($[M+Na]^+$) 361.2349, found: 361.2342.

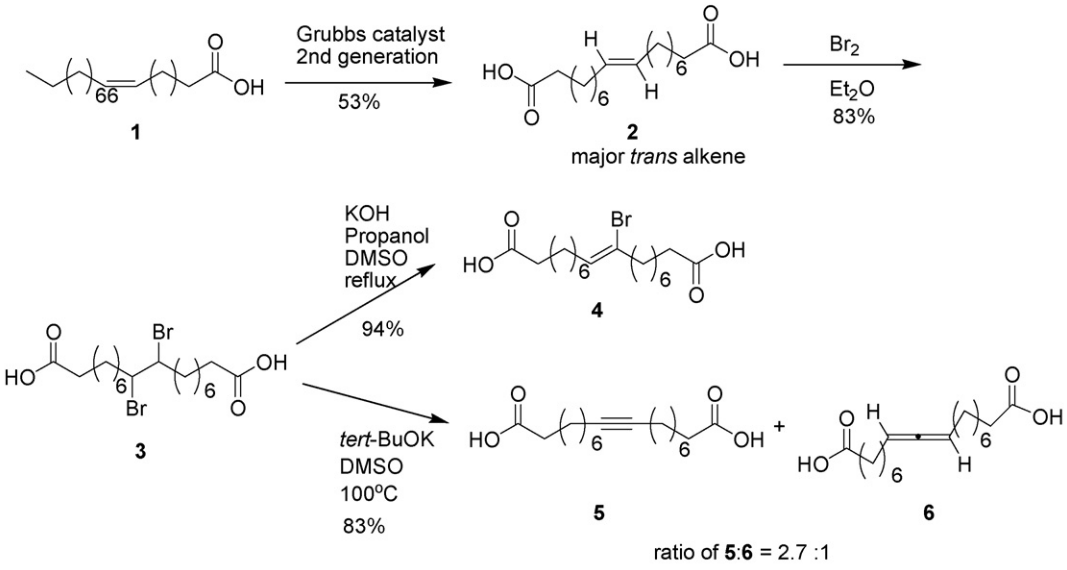
### *2.5. Allene-α,ω-dicarboxylic ester* ***8***

IR (Microscope) 1960 (C=C=C), 1741 (C=O) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 5.03 (quintet, 2H, $J = 4.8$ Hz, CH=C=CH), 2.28 (t, 2H, $J = 7.4$ Hz, $CH_2$–$COOCH_3$), 2.28 (t, 2H, $J = 7.5$ Hz, $CH_2$–$COOCH_3$), 1.98–1.91 (m, 4H, $CH_2$-CH=C), 1.64–1.56 (m, 4H, $CH_2$–$CH_2COOCH_3$), 1.42=1.26 (m, 16H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 203.8 (CH=*C*=CH), 174.2 (C=O), 174.1 (C=O), 90.9 (*C*H=C=CH), 90.7 (CH=C=*C*H), 51.4 ($CH_3$–O, two carbon overlap), 34.1, 34.0, 29.1, 29.09, 29.04, 28.95 (two carbon overlap), 28.92, 28.867, 28.861, 28.7, 24.91, 24.90; HRMS (ESI) calcd for $C_{20}H_{34}O_4Na$ ($[M+Na]^+$) 361.2349, found: 361.2356.

### *2.6. Aromatic hexa-ester* ***9***

To a solution of alkyne ester **7** (4.0 g, 11.8 mmol) in THF (50 mL) was added chlorotrimethylsilane (3.7 mL, 29.6 mmol) and Pd/C (500 mg). The reaction mixture was refluxed for 4 h and cooled to room temperature. The mixture was then filtered to remove Pd/C which was washed with ethyl acetate (50 mL). The resulting solution was further washed water (50 mL), brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated under the reduced pressure and the residue was purified by column chromatography to afford product **9** (3.5 g, 87% yield) as a colorless oil.

IR (Microscope) 1741 (C=O) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 3.67 (s, 18H, $CH_3$–O), 2.50–2.43 (m, 12H, $CH_2$Ph), 2.33 (t, 12H, $J = 7.4$ Hz, $CH_2$–$COOCH_3$), 1.65 (quintet, 12H, $J = 7.3$ Hz, $CH_2$–$CH_2COOCH_3$), 1.52–1.28 (m, 48H); $^{13}C$ NMR (125 MHz, $CDCl_3$) ( 174.2 (C=O), 136.5 (C=C), 51.4 ($CH_3$–O), 34.1, 31.6, 30.5, 29.8, 29.2, 29.1, 24.9; HRMS (ESI) calcd for $C_{60}H_{102}O_{12}Na$ ($[M+Na]^+$) 1037.7263, found: 1037.7250.



**Scheme 1.** Preparation of alkyne α,ω-dicarboxylic acid **5**.

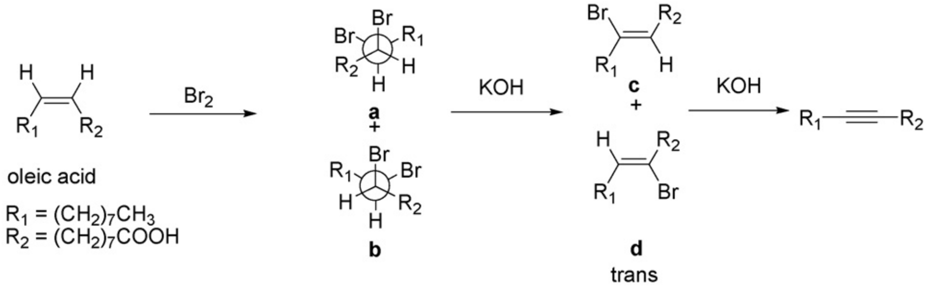
*2.7. Aromatic hexa-ol **10***

To a solution of hexa-ester **9** (270.0 mg, 0.3 mmol) in THF (10 mL) was added lithium aluminum hydride (88.2 mg, 2.3 mmol). The reaction mixture was stirred for 2 h. Then ethyl acetate (5 mL) and water (5 mL) was added to quench excess lithium aluminum hydride. The solution was diluted with ethyl acetate (30 mL) and 2N HCl was added until the solution became clear. The organic phase was separated and washed with water (20 mL), brine (20 mL) and dried over $MgSO_4$. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography to afford aromatic polyol (230 mg, 94% yield) as a colorless sticky oil. IR (Microscope) 3318 (OH) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 3.65 (t, 12H, $J$ = 7.6 Hz, $CH_2$–OH), 2.52–2.45 (m, 12H, $CH_2$Ph), 1.78 (brs, 6H, OH), 1.62–1.25 (m, 72H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 136.7 (C=C), 62.9 ($CH_2$–OH), 32.8, 31.4, 30.5, 29.7, 29.4, 29.3, 25.8; HRMS (ESI) calcd for $C_{54}H_{102}O_6Na$ ($[M+Na]^+$) 869.7568, found: 869.7574.

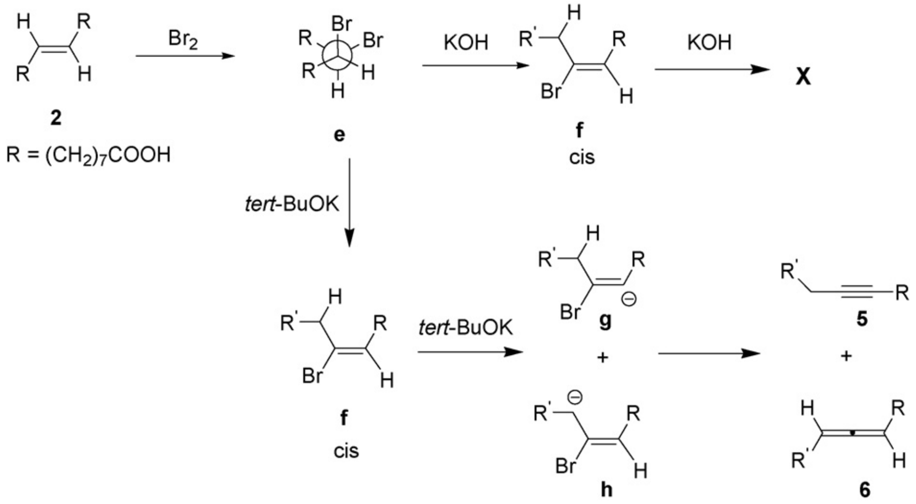
## 3. Results and discussion

Oleic acid, as an economic mono-unsaturated fatty acid, was used to synthesize unsaturated-α,ω-dicarboxylic acids. By solvent free self-metathesis, oleic acid was converted into unsaturated-α,ω-dicarboxylic acid **2** in the presence of second-generation Grubbs catalyst in 53% yield. The metathesis products consisted of the major *trans*-alkene and minor *cis*-alkene at a ratio of 91:9 by NMR spectrum (Scheme 1) (Ngo et al., 2006). Since **2** has very poor solubility in diethyl ether, THF was first chosen as the solvent. However, the bromination reaction in THF does not proceed satisfactorily. It would appear, from analysis of NMR spectra that THF participates in the reaction. Interestingly, when diethyl ether was used as the solvent, solid dicarboxylic acid **2** was slowly consumed with the addition of bromine to afford dibromide compound **3** in good yield. By subjecting dibromide **3** to basic conditions (Silbert, 1984; Augustin and Schafer, 1991) the only product isolated was vinyl bromide **4**. A tiny amount of desired alkyne **5** derived from the *cis*-isomer of compound **2** was observed from the NMR spectrum of the crude products. This amount remained unchanged when the reaction was left to stir overnight. Based on these observations; potassium hydroxide is not a strong enough base to effect the second HBr elimination. Therefore, potassium *tert*-butoxide in DMSO, a stronger base than KOH, was then tried. When dibromide compound **3** was heated with potassium *tert*-butoxide in DMSO, two inseparable isomers alkyne **5** and allene **6** were formed at a ratio of 2.7:1.

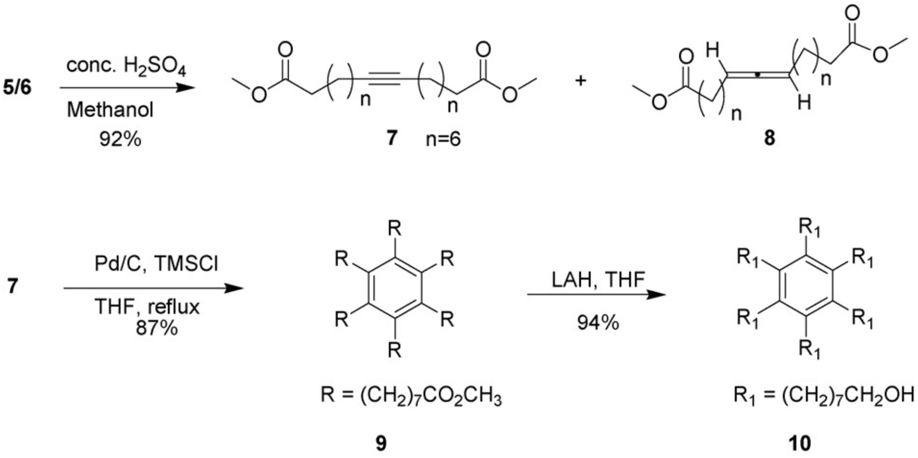
Comparing the mechanisms of bromination and dehydrobromination of *cis*-oleic acid and *trans*-unsaturated diacid **2**, an explanation for the formation of allene **6** can be given. When oleic acid was brominated, enantiomers **a** and **b** were produced (Scheme 2). Since brominated oleic acid is a non-symmetrical molecule, there will be two possible pathways for the first HBr elimination. Based on the rule of antiperiplanar elimination, the first HBr elimination of isomers **a** and **b** would result in olefin **c** and **d**. Both **c** and **d** are *trans*-olefins that make the second HBr elimination much easier based on the antiperiplanar elimination rule.



**Scheme 2.** Mechanism of dehyrobromination of oleic acid.



**Scheme 3.** Mechanism of dehydrobromination of *trans*-unsaturated diacid **2**.



**Scheme 4.** Preparation of aromatic hexa-ol **10**.

However, in the case of symmetric diacid **2**, bromination only gave one single isomer **e** (Scheme 3). After the first HBr elimination of isomer **e**, the *cis*-olefin **f** was obtained. Having obtained the *cis*-olefin, it is now quite difficult for the second HBr elimination to occur due to the weak basicity of KOH. When a stronger base, potassium *tert*-butoxide, is used, there are two possible acidic protons in isomer **f** that can be deprotonated. Deprotonation at these two sites can afford the corresponding carbanion intermediates **g** and **h**, which can then eliminate bromide to give desired alkyne **5** and undesired allene **6**.

The inseparable mixture of compounds **5** and **6** was first cyclotrimerized in the presence of palladium and TMSCl, however only 30% of the desired hexa-ol was obtained. Some side products were slowly generated as the reaction proceeded. This may be due to the presence of the allene impurity in the reaction since the allene may also form a complex with the palladium catalyst in a competing side reaction. In the crude NMR spectrum of the reaction mixture, two aromatic proton signals which may derive from allene moiety are observed above 7 ppm. Based on this observation, carboxylic groups of **5** and **6** were methylated with catalytic amount of concentrated sulfuric acid in methanol (Scheme 4). The resulting diester compounds **7** and **8** were separated by flash chromatography. The alkyne fatty ester was then trimerized to afford hexa-ester **9** in good yield (87%). Hexa-ester **9** was then reduced by the treatment of LAH to obtain hexa-ol **10** in excellent yield (94%).

In conclusion, we have reported a simple route for the synthesis of highly functional aromatic hexa-ol **10**. This general method can be applied to the synthesis of aromatic hexa-ols or hexa-cids from other simple unsaturated fatty acid.

## Acknowledgements

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